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EDITOR'S COMMENTARY

Emerging menu options for gonadal reincarnation

David F. Albertini

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For nearly a decade now, amidst the promises and purviews of regenerative medicine, the prospects for rehabilitation or replacement of tattered organs have resonated with those unwilling to accept the fate of their aging bodies. Your personal candidate for tissue replacement is often dictated by your genetics and some combination of luck–good or bad–that challenges your organs' abilities to withstand the test of time after years of use and abuse. Regenerative medicine is fast becoming a reality, and will likely debut on a commercial level as tractable tissue replacements for joints, blood vessels, and bladders, which are less complex, histologically-speaking. But anxious moments accrue for those whose replacement needs include the likes of hearts, brains, kidneys, and livers. What about your gonads?

The search for a fountain of youth when it comes to preserving or extending your reproductive ability reduces to a most fundamental biological principle: use it or lose it! Gonads carry the burden of performing two basic tasks during our reproductive lifespan and they do so on a continuous or discontinuous schedule. For males, the call of puberty enlightens the testes such that hormonal rhythms sustain the continuous process of spermatogenesis, yielding sufficient numbers of spermatozoa to meet the regular demands of a fully-loaded ejaculate. For females, on the other hand, the strategy of putting all the eggs in one basket (*sic* two ovaries) at birth leads to the discontinuous provision of a single mature oocyte at ovulation, the tell-tale outcome of periodic fluctuations in a hormonal conversation that took place between the brain and gonads. In both cases, germ plasm wastage is the norm, not the exception, with the vast majority of germ cells vanishing into an abyss not unlike the one that so many aspiring actors find themselves resolved to on the road to Broadway or Hollywood. Fortunately (or not), the one-on-one encounter of sperm and egg happens against all odds, accounting for our growing numbers on this planet. The less fortunate among us seek medical intervention for infertility treatment when and where available. Enter the world of fertility preservation.

2012 was indeed a remarkable year. The prospects for manipulating gonadal physiology and germ cell wastage were measurably advanced by a series of landmark papers, which spawned a journalistic feeding frenzy that captured the global attention of health specialists and the public at large. Fittingly, this was best evidenced by recognizing the breakthroughs of the 2012 Nobel Laureates in Physiology and Medicine, Sir John Gurdon and Professor Shinya Yamanaka. The notion that a nucleus from a differentiated cell could be coaxed back into a naïve or pluripotent state (a notion that became known as reprogramming) transitioned from an eclectic observation on amphibian oocytes in the 1960s to iconic status after the demonstration of induced pluripotent stem cell (iPSCs) production early in the 21st century.

To the matter of fertility preservation, a continuing special focus for JARG, three papers lead off this issue which set the stage for what is emerging as a central role for human ARTs in the field of regenerative medicine. Gonadotoxic therapies for management of cancer and hematological disorders in children pose one of the most serious threats to

Capsule Banking germ plasm that works–what we were endowed with- or fabricating gonads from scratch, sit soundly as potential menu options for future ARTs for patients whose ability to reproduce has been prevented by the failure of their gonads to make germ cells when they would most like to have them.

D. F. Albertini (✉)
University of Kansas Medical Center, Kansas City,
KS 66160, USA
e-mail: dalbertini@kumc.edu

future gonadal function and understandably test physicians seeking to retain some measure of reproductive fitness for their patients. From Kutluk Oktay's group comes a report on male and female children who were offered gonadal tissue cryopreservation during the course of various medically-indicated procedures. The findings illustrate how a successful team effort can be realized to minimize patient costs and risks, and afford an opportunity for restoration of gonadal function in their anticipated reproductive years of life. From Denmark comes an important study by Mikkel Rosendahl and colleagues in which cryopreserved ovarian tissues were transplanted into patients following gonadotoxic cancer treatments and biomarkers of functional restoration were apparent in many of the patients so treated. This work adds momentum to the importance of gonadal tissue cryopreservation for subsequent transplantation despite lingering concerns over reintroduction of disease and a recognized need to develop better methods and approaches for long term storage of ovarian or testicular biopsy material. Towards this end, we feature the paper by Sandra Sanfilippo and collaborators from several institutions who have tailored a novel slow-freeze formulation for ovarian tissue that alters both cryoprotectant and antioxidant components. In addition to evaluating follicular viability, the study uncovers important parameters of vascular endothelium and stromal compartments in thawed ovarian tissues that were subjected to an extended culture period, a measure of tissue functionality that had not been previously exploited and one that will likely set the stage for future investigations on tissue integrity prior to transplantation. Collectively, these papers emphasize the importance and applicability of gonadal reincarnation for patients who have the opportunity to undergo tissue cryopreservation with existing technology. It is fair then to ask whether other technologies loom on the horizon for recharging gonads that have endured complete or partial loss of germ plasm?

The matter of stem cells and gametes will be featured in the February issue of JARG but, most certainly, a crowning accomplishment reported late in 2012 has brought to the surface an intermingling of reproductive and regenerative medicine. From Kyoto University in Japan arrives the publication by Hayashi and colleagues ("Offspring from oocytes derived from in vitro primordial Germ cell-like cells in mice", Science, 4 October 2012 / Page 1 / 10.1126/science.1226889) describing closure of the circle of life between stem cells and female germ cells in the mouse, a repeat performance of their 2011 paper in Cell (doi:10.1016/j.cell.2011.06.052) when this was achieved in the male. The lessons obtained from this work are manifold. It is a technological *tour de force*, a roadmap for using developmental biology principles in experimental design, and a declaration for the expanding role that ARTs play in the field of regenerative medicine. The bottom line is that mouse embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs), converted into primordial germ cell-like cells when combined with age-appropriate ovarian somatic cells, assumed the characteristics of card-carrying oocytes. Proof of the pudding came in the form of demonstrating that oocytes retrieved from reconstituted ovaries transplanted into a "host" ovarian environment were capable of undergoing *in vitro* maturation and IVF, and produced viable offspring after embryo transfer. What distinguishes this work from the many other attempts to generate oocytes from various kinds of stem cells is the directness of the approach and its overall efficiency. Efforts to repeat this work are ongoing, and the implications it raises in terms of teasing apart the mechanistic attributes that confer reprogramming of ES or iPS lineages into the female germ line will surely raise our level of understanding of the biology of the oocyte in particular and the ovary more broadly.

Satisfying our curiosity about the underpinnings of germ cell mystique is but one likely outcome from the studies described in Tsutomu Saitou's work, as recently discussed by Hayashi *et al*.,(Fertility and Sterility, 2012; 97:1250–9). And, it would follow that some of the factors underlying infertility in men and women could be modeled through such an approach using stem cells of either embryonic or iPSC varieties from humans and other animals. What remains unknown, however, is the extent to which advances of this kind will be brought bear in a clinical setting. With the remarkable strides of the past year as a backdrop, there is much to anticipate in 2013 as the field of reproductive medicine contextualizes these and forthcoming discoveries with respect to new menu options in the human ART clinic, and the ethical and legal implications that will arise in the translation of basic science discoveries into clinical practice.

I urge our readership to prepare for a roller coaster ride into the future. And finally, note that this excursion will be facilitated by a number of additions to our Editorial Board who we are pleased will be joining the JARG family. Welcome to our new Associate Editors Clarisa Gracia, Lawrence C. Layman, and Elizabeth McGee, and new board members Paul Brezina, Sherman Silber, Anil Dubey, Daniel DeMatos, Hananel Holzer, Karla Hutt, and Armand Zini.

Best wishes for a healthy and productive 2013!